and for surface characteristics to define active sites and macromolecular contact sites, and defining at least one class of compounds predicted to have binding potency using the active sites information corresponding to the one target protein;

(i) developing a homology model using computational tools for homology model building and the refined model of the one target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool along with the developed homology model; and

(j) performing steps (f) through (i) for each of the other target proteins.--

REMARKS

Claims 1-12 are pending and presented for examination in the subject application. Applicants have hereinabove amended independent claims 1 and 7 to place them in better form for consideration.

Applicants maintain that no new matter and no new issues are presented by this amendment. Accordingly, applicants respectfully request that this Amendment be entered.

Rejection Under 35 U.S.C. § 103(a)

In Section 9 of the June 9, 2000 Final Office Action, claims 1, 3, 5-7, 9, 11 and 12 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bachar et al., Protein Engineering 6, 279-288, 1993 (hereinafter "Bachar paper") in view of Hendrickson et al., The EMBO Journal 9, 1665-1672, 1990 (hereinafter "Hendrickson paper").

The Examiner stated that claims 1, 3, 5-7, 9, 11 and 12 are drawn to a system and process for determining experimentally a plurality of three-dimensional atomic structures, each associated with a corresponding protein, first a protein database of

sequence information and known structural and functional information which is systematically organized, must be established for integration with at least one bioinformatics tool using the structural and functional information to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences. The Examiner also stated that a target protein is analyzed using sequence of the information corresponding to other family members of the database and information corresponding to other known three-dimensional structures which is stored in the database, with means for refining the model for functional motifs, and means for defining at least one class of compound predicted to have binding potency using the active site information.

The Examiner stated that the Bachar paper teaches a method/system for protein classification, wherein an experimentally-derived, three-dimensional structure of a target protein can be classified by assignment to a cluster set of structurally similar, three-dimensional representation of proteins in an organized database. The Examiner also stated that the design and organization of the database described in the Bachar paper consists of three major steps: 1) finding relatively small subset of the structures that form an initial match; 2) finding clusters of initial matches that represent similar transformations; and 3) extending the clusters to contain additional matching pair residues. The Examiner stated that these steps are further comprised of sub-steps described in the Bachar paper at pages 280-283. The Examiner stated that as a result of organizing a database and developing a means to utilize the database for similarity comparisons/clustering, one can determine a surface motif in a target protein, one can determine an activity of a given compound to the target protein, and one can objectively determine a number of chemical or biological properties of the target protein.

The Examiner acknowledge that although the Bachar paper utilizes data which represent the three-dimensional structures of proteins, the Bachar paper does not disclose a means for preparing proteins, a means of preparing protein crystals for analysis, a means of three-dimensional analysis, or any peripheral mean for data acquisition.

The Examiner stated that the Hendrickson paper from a similar field of endeavor teaches a system and process for incorporating selenomethionine (as a replacement for methionine) into recombinant proteins produced from plasmids in E. coli., which are crystallized and analyzed by multiwavelength anomalous diffraction (MAD) as a means for producing a three-dimensional representation of a target protein. The Examiner stated that the method described in the Hendrickson paper provides advantages over conventional x-ray techniques for elucidating three-dimensional protein structures, in that MAD utilizes the scattering effects of resonance between x-rays and bound atomic orbitals, it is perfectly isomorphic, allows for data sampling from a single crystal, and the analysis is algebraically exact.

The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the selenomethionyl protein expression technique for MAD analysis with the three-dimensional, protein structure classification method/process taught by the Bachar paper, because the Hendrickson paper teaches the aforementioned advantages of using the method/system described therein for recovering data sets representing the three-dimensional structure of proteins over conventional x-ray crystallographic methods. The Examiner alleged further that the invention as a whole was *prima facie* obvious at the time the invention was made.

Applicants maintain that the Bachar paper and the Hendrickson

paper do not render unpatentable the invention set forth in claims 1, 3, 5-7, 9, 11 and 12. The claimed invention is patentable over the Bachar paper and the Hendrickson paper for at least the following reasons.

The subject application provides a novel and unobvious method and system for determining experimentally, at a high throughput and on a large scale, a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein. Sequence information, as well as known structural information and functional information, for a plurality of proteins are systematically organized into a database, and the wealth of information, including in particular the sequence information, stored in the database is used with a bioinformatics tool to cluster the plurality of proteins into families. In each such family, the members have homologous sequences. Appropriately representative members of the families are selected as target proteins. The target proteins are synthesized, screened, processed and crystallized. The target proteins are synthesized in parallel and crystallized in parallel in order to supply specimen crystal at a rate sufficient to keep pace with the high-throughput crystallography performed on the specimen crystals. For each target protein, corresponding diffraction data obtained from the X-ray crystallography is analyzed and used to build and refine an atomic model of the target protein. The refined model is analyzed using, among others, sequence information, which are stored in the database, corresponding to other family members to determine functional motifs and surface characteristics to define active sites and macromolecular contact sites. The refined model also is used to develop a homology model which in turn is used to develop further the database. The method and system may be used to develop a comprehensive structural genomics database.

The Bachar paper relates to a method of comparing known protein structures in a sequence-independent manner. Each region of structural similarity between the structures is determined using three-dimensional (3-D) coordinate data of each known structure to be compared. The method described by the Bachar paper, as the Examiner pointed out, consists of the following major steps: (1) finding relatively small subsets of the structures that form an initial match; (2) finding clusters of initial matches that represent similar transformations; and 3) extending the clusters to contain additional matching pair residues.

The Bachar paper appears to describe a database of known protein structures. The Bachar paper does not describe or suggest, however, maintaining in the database sequence information for the proteins. Indeed, the Bachar paper emphasizes that the method of comparing known protein structures described therein is **sequence-independent**. Thus, while the Bachar paper appears to describe clustering proteins with similar known structures, the Bachar paper neither describes nor suggests, and indeed actually teaches away from, clustering a plurality of proteins into a plurality of families, in which members of each family have corresponding **homologous sequences**, using **sequence information**, structural information and functional information stored in the database, as provided by the claimed invention in the subject application. Also, the Bachar paper teaches away from analyzing the refined model, stored in the database, of the target protein using **sequence information** corresponding to other family members which is stored in the database, as provided by the claimed invention in the subject application.

Further, while the Bachar paper appears to describe matching known protein structures, it does not describe or suggest a system and method for performing **structure determination experimentally**, nor even another means for developing a

comprehensive structural genomics database in which proteins are organized into families. Moreover, the Bachar paper neither describes nor suggests, as the Examiner acknowledged, at least the following features of the claimed invention: (i) synthesizing for each family a plurality of target proteins, in parallel, which are appropriately representative members of the family, using information stored in the database corresponding to the target proteins; and (ii) performing high-throughput crystallography, including measuring for diffraction data the suitable specimen crystals of the target protein, building an atomic model of the target protein according to an analysis of the diffraction data, and refining the model of the target protein against the diffraction data and storing the refined model in the database.

The present invention provides a process and system that may be used to develop a comprehensive protein database which may be utilized for, e.g., target identification. One of ordinary skill in the art at the time of the invention would not have been motivated to look to the Bachar paper for teachings towards that end since the Bachar paper describes comparing known protein structures, but simply does not teach or suggest adapting its teachings for determining the structure of other proteins.

Further, in order to cover the genomics space, the present invention provides for systemmatically organizing the already available information, including in particular the wealth of sequence information, of the proteins into a database, and using the information with a bioinformatics tool to cluster proteins into families in which members have homologous sequences. The Bachar paper simply does not show, and indeed teaches away from, a recognition that the sequence information may be used for characterization of the families. Thus, one of ordinary skill in the art at the time of the invention would not have been

motivated to combine the teachings of the Bachar paper with any prior art that teaches using sequence information for that end.

The Hendrickson paper relates to a system and process for expressing a recombinant selenomethionyl protein (thioredoxin) in *E.coli*. Selenomethionyl thioredoxins produced by the system and process were crystallized and characterized, and then analyzed through X-ray crystallography using a multiwavelength anomalous diffraction (MAD) phasing technique.

The Hendrickson paper does not describe or suggest, however, performing structure determination experimentally on a large scale, nor the benefit of maintaining a comprehensive database of sequence information, structural information and functional information for a plurality of proteins for achieving that end. The Hendrickson paper does not describe or suggest, for example, (i) systematically organizing sequence information, and known structural information and functional information, for a plurality of proteins into a database, (ii) clustering a plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences, using sequence information, structural information and functional information stored in the database, and (iii) synthesizing for each family a plurality of target proteins, in parallel, which are appropriately representative members of the family, using information stored in the database corresponding to the plurality of target proteins, as provided by the claimed invention in the subject application.

Also, while the Hendrickson paper describes obtaining diffraction data from the X-ray crystallography experiments, there is no description or suggestion in the Hendrickson paper of (i) building an atomic model of the target protein according to an analysis of the diffraction data, refining the model of the

target protein against the diffraction data, and storing the refined model in the database, (ii) analyzing the refined model, stored in the database, of the target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database, (iii) developing a homology model using computational tools for homology model building and the refined model of the one target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool along with the developed homology model, and (iv) repeating these steps for each of other target proteins, as provided by the claimed invention in the subject application.

Thus, neither the Bachar paper nor the Hendrickson paper describes or suggests performing structure determination experimentally on a large scale in order to develop a comprehensive structural genomics database. Moreover, a combination of the teachings of the Bachar paper and the Hendrickson paper does not render unpatentable the claimed invention because neither the Bachar paper nor the Hendrickson paper describes or suggests, for example, a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of sequence information, and known structural information and functional information, which is systematically organized for a plurality of proteins; (ii) at least one bioinformatics tool using the structural information, sequence information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool

a plurality of target proteins, in parallel, which are appropriately representative members of the family, using information stored in the database corresponding to the target proteins; (iv) X-ray crystallography means having means for building an atomic model of the target protein according to an analysis of the diffraction data, and means for refining the model of the target protein against the diffraction data and storing the refined model in the database; and (v) structure extraction means having means for analyzing the refined model of the target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database, as provided by the invention set forth in twice amended claim 1.

Similarly, a combination of the teachings of the Bachar paper and the Hendrickson paper does not render unpatentable the claimed invention set forth in claim 7 because neither the Bachar paper nor the Hendrickson paper describes or suggests a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) systematically organizing sequence information, and known structural information and functional information, for a plurality of proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (c) synthesizing for each family determined in step (b) a plurality of target proteins, in parallel, which are appropriately representative members of the family, using information stored in the database corresponding to the plurality of target proteins; (g) performing high-

throughput crystallography, including building an atomic model of the one target protein according to an analysis of the diffraction data, refining the model of the one target protein against the diffraction data, and storing the refined model in the database; and (h) analyzing the refined model, stored in the database in step (g), of the one target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database.

Regarding claims 3, 5 and 6, applicants respectfully point out that claims 3, 5 and 6 depend on and include all the limitations of claim 1. Thus, claims 3, 5 and 6 are patentable at least for the reasons set forth above with respect to claim 1.

Regarding claims 9, 11 and 12, applicants respectfully point out that claims 9, 11 and 12 depend on and include all the limitations of claim 7. Thus, claims 9, 11 and 12 are patentable at least for the reasons set forth above with respect to claim 7.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 3, 5-7, 9, 11 and 12 under 35 U.S.C. §103(a).

Rejection Under 35 U.S.C. § 103(a)

In Section 10 of the June 9, 2000 Final Office Action, claims 4 and 10 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Bachar paper and the Hendrickson paper, as applied to claims 1, 3, 5-7, 9, 11 and 12 above, and further in view of Lima et al. *Structure 5, 763-774, 1997* (hereinafter "Lima paper").

The Examiner stated that claims 4 and 10 are drawn to the system

and process of claims 1 and 7, respectively, wherein the synchrotron storage ring has undulator beamlines for use with MAD.

The Examiner acknowledged that neither the Bachar paper nor the Hendrickson paper teaches a synchrotron storage ring which has undulator beamlines for use with MAD.

The Examiner stated that the Lima paper teaches using an undulator beamline x-ray source, with MAD because of the high output levels, with narrow, tunable, harmonic peaks.

The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the inventions was made to utilize the undulator beamline x-ray source, in place of the synchrotron device as taught by the Hendrickson paper, because the Lima paper demonstrates a high output x-ray source, with narrow, tunable, harmonic peaks. The Examiner alleged that the invention as a whole was *prima facie* obvious at the time the invention was made.

Applicants maintain that the Bachar paper, the Hendrickson paper and the Lima paper do not render unpatentable the invention set forth in claims 4 and 10. The claimed invention is patentable over the Bachar paper, the Hendrickson paper and the Lima paper for at least the following reasons.

As stated above, the Bachar paper and the Hendrickson paper fail to describe or suggest a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of sequence information, and known structural information and functional information, which is systematically organized for a plurality of proteins; (ii) at

least one bioinformatics tool using the structural information, sequence information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool a plurality of target proteins, in parallel, which are appropriately representative members of the family, using information stored in the database corresponding to the target proteins; (iv) X-ray crystallography means having means for building an atomic model of the target protein according to an analysis of the diffraction data, and means for refining the model of the target protein against the diffraction data and storing the refined model in the database; and (v) structure extraction means having means for analyzing the refined model of the target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database, as provided by the invention set forth in twice amended claim 1 from which claim 4 depends.

The Bachar paper and the Hendrickson paper also fail to describe or suggest a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) systematically organizing sequence information, and known structural information and functional information, for a plurality of proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (g) performing high-

throughput crystallography, including building an atomic model of the one target protein according to an analysis of the diffraction data, refining the model of the one target protein against the diffraction data, and storing the refined model in the database; and (h) analyzing the refined model, stored in the database in step (g), of the one target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database, as provided by the invention set forth in twice amended claim 7 from which claim 10 depends.

The Lima paper describes a process using MAD analysis for determining the three-dimensional structure of fragile histidine triad (FHIT) protein. The Lima paper describes use of an undulator beamline x-ray source.

The Lima paper, like the Bachar paper and the Hendrickson paper, does not describe or suggest, however, at least the following features set forth in claim 1, from which claim 4 depends: (i) a database of sequence information, and known structural information and functional information, which is systematically organized for a plurality of proteins; (ii) at least one bioinformatics tool using the structural information, sequence information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences; and (iii) structure extraction means having means for analyzing the refined model of the target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database.

The Lima paper, like the Bachar paper and the Hendrickson paper,

also fails to describe or suggest at least the following features set forth in claim 7, from which claim 10 depends: (a) systematically organizing sequence information, and known structural information and functional information, for a plurality of proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (c) synthesizing for each family determined in step (b) a plurality of target proteins, in parallel, which are appropriately representative members of the family, using information stored in the database corresponding to the plurality of target proteins; and (h) analyzing the refined model, stored in the database in step (g), of the one target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database

Therefore, even a combination of the Lima paper with the Bachar paper and the Hendrickson paper in the manner suggested by the Examiner fails to teach or render obvious all features of the claimed invention.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 4 and 10 under 35 U.S.C. §103(a).

Rejection Under 35 U.S.C. § 103(a)

In Section 11 of the June 9, 2000 Final Office Action, claims 2 and 8 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Bachar paper and the Hendrickson paper, as applied to claims 1, 3, 5-7, 9, 11 and 12 above, and further in

view of U.S. Patent No. 5,525,198 issued to Craig et al. (hereinafter "Craig '198).

The Examiner stated that claims 2 and 8 are drawn to the system and process of claims 1 and 7, respectively, wherein a cryogenic freezing means is used to freeze the target protein crystal.

The Examiner acknowledged that neither the Bachar paper nor the Hendrickson paper disclose the use of cryogenic freezing means to freeze the target protein crystal.

The Examiner stated that Craig '198 teaches the cryogenic freezing of target protein crystals as a means of increasing the crystal's stability during exposure to x-ray sources.

The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a means for the cryogenic cooling of the target protein crystal, with the system/process described in the Bachar paper, in view of the Hendrickson paper, and Craig '198, since Craig '198 teaches that cryogenic cooling preserves crystals during x-ray sampling. The Examiner alleged that the invention as a whole was *prima facie* obvious at the time the invention was made.

Applicants maintain that the Bachar paper, the Hendrickson paper and Craig '198 do not render unpatentable the invention set forth in claims 2 and 8. The claimed invention is patentable over the Bachar paper, the Hendrickson paper and Craig '198 for at least the following reasons.

As stated above, the Bachar paper and the Hendrickson paper fail to describe or suggest a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at

least the following: (i) a database of sequence information, and known structural information and functional information, which is systematically organized for a plurality of proteins; (ii) at least one bioinformatics tool using the structural information, sequence information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool a plurality of target proteins, in parallel, which are appropriately representative members of the family, using information stored in the database corresponding to the target proteins; (iv) X-ray crystallography means having means for building an atomic model of the target protein according to an analysis of the diffraction data, and means for refining the model of the target protein against the diffraction data and storing the refined model in the database; and (v) structure extraction means having means for analyzing the refined model of the target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database, as provided by the invention set forth in twice amended claim 1 from which claim 2 depends.

The Bachar paper and the Hendrickson paper also fail to describe or suggest a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) systematically organizing sequence information, and known structural information and functional information, for a plurality of proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which members of each family have corresponding

homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (c) synthesizing for each family determined in step (b) a plurality of target proteins, in parallel, which are appropriately representative members of the family, using information stored in the database corresponding to the plurality of target proteins; (g) performing high-throughput crystallography, including building an atomic model of the one target protein according to an analysis of the diffraction data, refining the model of the one target protein against the diffraction data, and storing the refined model in the database; and (h) analyzing the refined model, stored in the database in step (g), of the one target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database, as provided by the invention set forth in twice amended claim 7 from which claim 8 depends.

Craig '198 relates to determination of the 3-D structure of a molecule by forming an electrorheological crystalline mass of the molecule, obtaining an X-ray diffraction pattern of the electrorheological crystalline mass, and calculating the 3-D structure of the molecule using the X-ray diffraction pattern. Craig '198 was cited by the Examiner for its description of cryogenic freezing of target protein crystals as a means of increasing the crystal's stability during exposure to x-ray sources.

Craig '198, like the Bachar paper and the Hendrickson paper, does not describe or suggest, however, at least the following features set forth in claim 1, from which claim 2 depends: (i) a database of sequence information, and known structural information and functional information, which is systematically organized for a

plurality of proteins; (ii) at least one bioinformatics tool using the structural information, sequence information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences; (iii) X-ray crystallography means having means for building an atomic model of the target protein according to an analysis of the diffraction data, and means for refining the model of the target protein against the diffraction data and storing the refined model in the database; and (iv) structure extraction means having means for analyzing the refined model of the target protein using sequence information corresponding to other family members which is stored in the database and information corresponding to other known three-dimensional structures which is stored in the database.

Craig '198, like the Bachar paper and the Hendrickson paper, also fails to describe or suggest at least the following features set forth in claim 7, from which claim 8 depends: (a) systematically organizing sequence information, and known structural information and functional information, for a plurality of proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (g) performing high-throughput crystallography, including building an atomic model of the one target protein according to an analysis of the diffraction data, refining the model of the one target protein against the diffraction data, and storing the refined model in the database; and (h) analyzing the refined model, stored in the database in step (g), of the one target protein using sequence information corresponding to other family members which is stored in the database and information

corresponding to other known three-dimensional structures which is stored in the database

Therefore, even a combination of Craig '198 with the Bachar paper and the Hendrickson paper in the manner suggested by the Examiner fails to teach or render obvious all features of the claimed invention.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 2 and 8 under 35 U.S.C. §103(a).

In view of the amendments to the claims and remarks hereinabove, applicants maintain that claims 1 through 12 are now in condition for allowance. Accordingly, applicants earnestly solicit the allowance of claims 1 through 12.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee, other than the fee for the two-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box AF, Washington, D.C. 20231.

11/9/04

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Date